Claims 72-76, 80-86, 93-95, 125-129, 133-139, and 146-148 were rejected over Handsfield in view of Urquhart (US 4,851,231), and Edgren (US 4,522,625) in further view of Etienne (US 4,755,385) and Periti. Hansfield, Urquhart and Edgren and Periti appeared to be cited for the same reasons as in the prior Office Action. The Examiner further stated, in pertinent part, that

> The prior art discloses that azithromycin is effective for treating uncomplicated gonorrhea and drugs such as erythromycin, that induce nausea and vomiting should be administered to the intestine over time. The difference between the prior art and the claimed invention is that the prior art does not expressly disclose the in vitro criteria of Q0.25, Q1, Q2, Q4, and Q6 as determined by the claimed testing parameters. However, the prior art suggests the same as the prior art discloses that although erythromycin and azithromycin do have their differences, both erythromycin and azithromycin exhibit adverse gastric effects and are acid unstable (although azithromycin does have increased acid stability over erythromycin) and that resistant to gastric juices means that the preparation should release virtually no active substance for a period between 30 minutes and 2 hours and having a pH solubility of between 5.5 and 6.8 or which releases the active substance at a pH of between 5.5 and 6.8, preferably, between 6.0 and 6.4. As such, it would have been well within the skill of and one of ordinary skill in the art would have been motivated to control the release of azithromycin to be releases at least 30 minutes after ingestion so as to avoid adverse gastric effects and any acid instability by using an enteric coating which dissolves preferably at a pH of between 6.0 and 6.4. As such, one of ordinary skill in the art would expect that for enteric coatings which dissolve at pHs of greater than 6.0 that substantially no active agent will be released until the pH of the surrounding media, whether in vitro or in vivo, is at the appropriate pH. As such, such a dosage form will meet the criteria set forth in the claims. [Office Action, Paragraph bridging pages 3 and 4]

Applicants' Traversal

Applicants offer the following observations and comments in traversal of the rejection.

1. The Examiner cited Handsfield, Urquhart, and Edgren for the same reasons as in prior Office Actions. Office Action, page 2, 3rd full paragraph. None of these three references relates to azithromycin in a controlled release dosage form. Edgren and Urquhart are simply examples of controlled release dosage forms, but with no disclosure relating to azithromycin in any form of controlled release device. Handsfield simply demonstrates that azithromycin is a good, effective antibiotic.

2. Etienne adds nothing to the collective disclosures of Handsfield, Urquhart, and Edgren because Etienne relates to enteric coated dosage forms, not to sustained release dosage forms as required by the instant claims. A sustained release dosage

form is one that meters drug slowly relative to an immediate release dosage form and which generally commences its slow release essentially upon (or shortly following) swallowing.

3. The instant claims do not embrace enteric dosage forms. An enteric dosage form is one wherein an active ingredient, usually incorporated into an immediate release core also containing other components such as excipients, is protected by surrounding the core with a coating of an enteric polymer. Enteric coatings are designed to protect the active ingredient by separating and isolating the active from the low, acid pH of the gastric environment, including the stomach. As the dosage form reaches the higher pH intestinal environment, the enteric coating dissolves and the drug is immediately released from the core. Thus an enteric coated dosage form functions ideally at low pH by not releasing any drug, and at high pH (i.e., pH 5-6 or higher, the pH of an intestinal environment) by releasing immediately. Neither stage characterizes Applicants' claimed sustained release dosage forms. Applicants release in a sustained manner at low pH (as opposed to the "no release" stage of the enteric coated dosage form) and in a sustained release manner at high pH (as opposed to an immediate release stage).

4. The Examiner took the following position based on the prior art:

...resistant to gastric juices means that **the preparation should release virtually no active substance for a period between 30 minutes and 2 hours** and having a pH solubility of between 5.5 and 6.8 or which releases the active substance at a pH of between 5.5 and 6.8, preferably, between 6.0 and 6.4. As such, **it would have been well within the skill of and one of ordinary skill in the art would have been motivated to control the release of azithromycin to be releases at least 30 minutes after ingestion so as to avoid adverse gastric effects and any acid instability by using an enteric coating which dissolves preferably at a pH of between 6.0 and 6.4.** As such, one of ordinary skill in the art would expect that for enteric coatings which dissolve at pHs of greater than 6.0 that substantially no active agent will be released until the pH of the surrounding media, whether in vitro or in vivo, is at the appropriate pH. As such, such a dosage form will meet the criteria set forth in the claims. [Office Action, text bridging pages 3 and 4, emphasis supplied]

Regardless of whether it would be obvious to make an enteric coated dosage form as contended by the Examiner, however, Applicants' claims do not embrace enteric forms. The Examiner, for example, commented that "... the preparation should release virtually no active substance for a period between 30 minutes and 2 hours..." (see the first three lines of the quotation above). By contrast, Applicants' dosage form, as claimed in claim 72 can release up to 200 mg of azithromycin in just the first 15 minutes ($Q_{0.25}$). The dosage form claimed in claim 125 can release up to 4 mg/Kg of mammal weight in the

first 15 minutes, equating to a release of 200 mg/Kg for a reasonably sized mammal of 50 Kg. Thus, and in line with the Examiner's own observations, Applicants' sustained release dosage form releases azithromycin during the time period that an enteric dosage form would not release at all. In different words, prior art such as Etienne represents a distinct and direct teaching away from the claimed invention.

5. Applicants further note that the Examiner's rationale underlying the rejection, based on the Periti article, was grounded in the contention that the prior art discloses azithromycin as being acid sensitive. Applicants respectfully submit that the prior art is at best inconclusive as to whether azithromycin is acid sensitive and also as to whether placing it in an enteric dosage form would serve any purpose. See E. F. Fiese and S. H. Steffen, Journal of Anrimicrobial Chemotherapy, 1990, 25, Suppl. A, pp 39-47, copy enclosed as Exhibit A. The Fiese et al. article states in the Abstract that

> In addition at 37°C and pH 2 with ionic strength $\mu = 0.02$ azithromycin was degraded with a $T_{1/10}$ of 20·1 min while erythromycin underwent 10% decay in only 3-7 sec.

Again, Fiese clearly supports Applicants position that the differences in acid stability between azithromycin and erythromycin are so marked that no firm conclusion as to the utility of a protective enteric coating for azithromycin can be drawn based on erythromycin. Fiese et al in fact recognized this (in fact referring to azithromycin's "inherent acid stability"!) when it was stated (see the next to last sentence before the end of the article, on page 46):

> The inherent acid stability of azithromycin suggests that an enteric formulation may not be necessary.

Clearly, the subject matter taken as a whole (in this case azithromycin sustained release dosage forms), particularly in view of all of the prior art would not have been obvious. Fiese et al underscore that exact point.

6. In summary, Applicants respectfully submit that their claimed azithromycin sustained release dosage forms are not obvious over references that (1) relate to controlled release other than sustained release, and not to azithromycin or (2) relate to azithromycin, but not to sustained release. Applicants' position is: the fact that something could be done does not make it obvious to do so absent the appropriate teachings based in the prior art. In the instant case, there is simply no teaching in any of

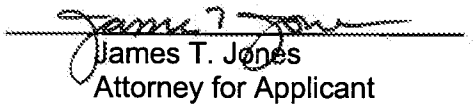
the references, including any combination thereof, that would lead or guide one of ordinary skill in the art to implement a sustained release form of azithromycin.

In regard to the rejection for obvious-type double patenting, Applicants respectfully disagree with the Examiner's comments and reasoning. It is respectfully submitted that the claims of the instant application are not obvious over the claims of US 6,068, 859. However, in an effort to expedite prosecution, a suitable terminal disclaimer has been included which addresses the issue cited by the Examiner, namely the possibility of separate ownership of US 6,068,859 and any patent issuing on the instant application.

It is accordingly respectfully submitted that all of the above rejections should be withdrawn, and that no other issues remain outstanding in this application. In view of the foregoing comments and amendments, this case is believed to be in condition for allowance, and a Notice of Allowance is courteously solicited.

Respectfully submitted,

Date: Aug 6, 2007



James T. Jones
Attorney for Applicant
Reg. No. 30,561

Pfizer Inc
Patent Department
Eastern Point Road
Groton, CT 06340
(860) 441-4903